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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/793,408	06/03/97	CHOO Y	235540/HCH/M

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EXAMINER	
SANDALS, W	
ART UNIT	**PAPER NUMBER**
1805	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/793,408	Applicant(s) Choo And Klug
	Examiner WILLIAM SANDALS	Group Art Unit 1805

☒ Responsive to communication(s) filed on *Jun 3, 1997* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-42* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-42* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 371 (c) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

The instant application has been amended to refer to the application PCT/GB95/01949, but fails to reference the prior applications which are listed in the Declaration.

Specification

2. The use of the trademark SOFTMAX and KALEIDAGRAPH has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

3. A substitute specification is required for pages 14, 44, 45 and 46 because the copies of the pages in the instant specification have not reproduced the entire page. The substitute specification

filed must be accompanied by a statement that it contains no new matter. Such statement must be a verified statement if made by a person not registered to practice before the Office.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Sequences appear in the Figures 2, 3, 4, 6, 7 and 15 which are not listed in the Brief Description of the Drawings. Sequences appear in Table 1 which are not identified by SEQ ID NO:'s. Sequences appear at page 24, lines 10 and 11, page 36, line 28, page 38, line 2, page 43, lines 28, 29 and 30 and page 45, line 14 which are not identified by SEQ ID NO:.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

5. Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Teachings on how to practice the claimed treatment of cancer are not present in the specification which are critical or essential to the practice of the invention. Said teachings are not included in the claim(s) and not enabled by the disclosure. *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The claim is drawn to a method of treating cancer, comprising delivering to a patient, or causing to be present therein, a zinc finger polypeptide which inhibits the expression of a gene enabling cancer cells to divide. While applicants have shown the expression of zinc finger polypeptides in cells in culture, they have not demonstrated any treatment of cancer. In order to do so , undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve development of protocols for treatment of many different types of cancers since the causes of cancer are known to be of biochemical, chemical, hereditary, environmental and viral origins, for example; mouse mammary tumors are caused by virus, which may also be transmitted by heredity, lung cancer caused by cigarette smoke and skin cancer caused by exposure to ultra violet rays.

b- Prophetic guidance is provided in a general teaching of how one of skill in the art would introduce a vector expressing a zinc finger polypeptide into a patient, but no guidance is provided on how one of skill in the art would proceed with treatment of cancer once this is accomplished. No information is provided on direct delivery of a zinc finger polypeptide into a patient for treatment of cancer.

c- No working examples are provided.

d- The nature of the invention is complex. Introduction of a vector into a patient (gene therapy) is an unpredictable art as described in Orkin (see the section on "Cancer", and the section entitled "Gene Therapy in man Status of the Field"). Efficacy has not been established and many problems still exist in gene therapy for example, adverse short term effects may alter the outcome and clinical experience is limited so long-term effects cannot be identified. There may be low frequency of gene delivery to the target site in the host which will affect the levels of a product to be expressed, and thus, the outcome of the therapy. Also, animal studies are frequently unreliable for prediction of outcome as is host response to the vector and/or the gene or gene product (i.e. immune responses and instability of the vector in the host and difficulty of delivery of the vector to the target in the host).

e- The prior art as recited in Blaese et al. (see especially pages 291, 294 and 296) taught that gene therapy is an art with many unknowns such as low transduction frequency of the vector at the desired host site as in the case of retrovirus, rapid loss of expression of the desired gene as in the case of adenovirus, the development of replication incompetent viral vectors, and even the

delivery of a vector into a patient may involve extensive trial and error experimentation to determine the best mode.

f- The unpredictability of gene therapy is very high, as exemplified in the state of the art as taught in Orkin and Blaese et al. supra.

g- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

6. Claims 15-29 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA, does not reasonably provide enablement for any nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to methods and kits for altering gene expression in a nucleic acid. While applicants have shown that the zinc finger polypeptides can interact with DNA, they have not demonstrated the ability of the zinc finger polypeptides to interact with any nucleic acid. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve development of assays for zinc finger polypeptides which bind nucleic acids such as DNA and RNA.

b- Guidance is provided for making a zinc finger polypeptide which binds to DNA.

c- Working examples are provided for making a zinc finger polypeptide which binds to DNA.

d- The nature of the invention is complex. Making zinc finger polypeptides which bind to DNA is a new and developing art.

e- The prior art taught by Friesen et al. (see especially the abstract) described making zinc finger polypeptides which bind to DNA, and did not teach binding to nucleic acids such as RNA. Friesen et al. taught that the factors which allow prediction of binding of zinc fingers to DNA do not apply to RNA.

f- The state of the art was concerned with zinc finger binding to DNA and did not discuss the factors which affected RNA binding.

g- Friesen et al. taught that making zinc finger polypeptides which bind to RNA was not predictable.

g- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

7. Claims 23-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cells in culture, does not reasonably provide enablement for any cell. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. 2d, 42(1).

The claims are drawn to a method to alter expression of a gene in a target cell comprising determining at least a part of a DNA sequence of the structural region and/or the regulatory region of a gene of interest, and designing a zinc finger polypeptide, and causing the polypeptide to be present in the target cell. While applicants have shown a method to alter expression of a gene in a target cell in culture, they have not demonstrated a method to alter expression or a gene in any target cell. In order to do so , undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would have involved developing protocols for introduction of a zinc finger polypeptide into any cell, determining a structural and/or regulatory region of a gene of interest and designing a zinc finger polypeptide which binds to said region of a gene of interest.

b- Guidance was provided for one of skill in the art to introduce a vector expressing a zinc finger polypeptide into a target cell in culture with minimal guidance for practicing the invention

in cells in an animal. No guidance was provided to introduce a zinc finger polypeptide into a cell or an animal.

c- Working examples were provided for cells in culture which include introduction of a vector expressing a zinc finger polypeptide into a target cell in culture. No examples were provided for practicing the invention in cells in an animal. No examples were provided to introduce a zinc finger polypeptide into a cell in culture or a cell in an animal.

d- The nature of the invention is complex. Zinc fingers targeted to the structural region and/or the regulatory region of a gene of interest are a new and developing art.

e- The prior art as described by Schatz et al. (see the abstract and column 1, line 25 to column 3, line 3), Jamieson et al. (Biochem. Vol. 33:5689-5695) (see especially the introduction) and Rebar et al. (see page 673, last paragraph) taught that polypeptides binding to a targeted region of a gene of interest is a rapidly developing art which was practiced exclusively *in-vitro* and in cells in culture, and delivery of a zinc finger polypeptide to an animal host is not described.

f- State of the art problems as taught by Orkin et al. and Blaese et al. in targeting a vector which expresses a zinc finger polypeptide to the desired cell in a host have been described supra, and include, host immune responses, getting the vector which expresses zinc finger polypeptide to the DNA of a cell, host immune responses to the vector or the zinc finger polypeptide expressed in the cell, possible expression and activity in undesirable cellular locations in the host and instability of the vector and/or the zinc finger polypeptide in the host.

g- Due to the lack of guidance in the instant application and in the prior art for making the claimed invention and the difficulties recited supra, practice of the claimed invention would have been unpredictable.

h- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

8. Claims 37-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The term "a disease-associated gene" is broad and poorly defined in the specification. The generic class of genes known as "oncogenes" such as Ras are well known to have many functions in a normal cell, and may or may not be "disease-associated". Further, the term "disease-associated gene" encompasses many genes which may or may not be well defined by the art.

9. Claims 4, 7-13, 16-17, 37-39 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 4, line 1 and claim 11, line 4, recite "a form suitable for use", and it is not explained what constitutes suitableness. If the definition of the above term is merely that condition necessary to produce the intended result, the use of this term is redundant.

11. Claim 4, lines 1-2, recites "A library ...in a form suitable for cloning as a fusion with the minor coat protein of bacteriophage fd". The term "library" refers to a DNA library described in claim 7. DNA is not customarily fused to a protein, and no guidance is provided for this in the claims or specification. If applicants meant that the DNA library of claim 7 should be fused to the DNA encoding the minor coat protein of bacteriophage fd, then the claims should be so amended.

12. The term "preferred ("optimal" in claim 10) binding" in claim 7, line 8, claim 8, line 18, claim 9, line 20 and claim 10, line 6 is not explained what constitutes "preferred" ("optimal"). If the definition of the above term is merely that condition necessary to produce the intended result, the use of this term is redundant.

13. In claims 12-13, 16-17, 37-39 and 41 the phrase "capable of" renders the claim(s) indefinite because the capacity of a compound to perform some function is merely a latent characteristic of said compound and said language carries no patentable weight. See MPEP § 2173.05(b), (d) and (g).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-29 and 31-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jamieson et al. in view of Rebar et al., Thiesen et al., Jacobs, Nardelli et al. and Desjarlais et al..

The claims are drawn to a library of DNA sequences encoding zinc finger polypeptides, with at least 3 zinc fingers, where at least the zinc finger 2 is partially randomized at positions -1, +2, +3 and +6, and at least one of +1, +5 or ++8, with +1 being the first amino acid of the alpha helix of the zinc finger. The zinc finger may be Zif268, and may be expressed as a phage display, and methods of designing and selecting the zinc fingers which bind to specific target DNA sequences (triplets), or nucleic acids of interest, which may be GCAGAAGCC or GACGGCGCC, or regulatory or structural regions of genes, which may be introduced into cells. The DNA or phage may immobilized on solid supports such as microtiter plates, magnetic or non-magnetic beads or particles, and affinity columns. Also claimed are kits for the use of the invention supra. Additionally claimed are methods of treatment of cancer, methods of modifying a nucleic acid, methods of inhibiting the expression of a disease-associated gene which may be an oncogene which may be BCR-ABL or Ras, and methods of detection.

Jamieson et al. taught (see the entire article, especially the introduction and abstract) a library of DNA sequences encoding zinc finger polypeptides, with at least 3 zinc fingers, where at least the zinc finger 1 (finger 2 is taught as a target for modification at page 5694, last paragraph) is partially randomized at positions -1, +2, +3 and +6, and taught that the positions +1, +5 or ++8, were known to be randomized in a collection of naturally occuring zinc fingers, (with +1 being the first amino acid of the alpha helix of the zinc finger). Jamieson et al. taught The zinc

finger may be Zif268, and was expressed as a phage display, and methods of designing and selecting the zinc fingers which bind to specific target DNA sequences (triplets), or nucleic acids of interest, or regulatory or structural regions of genes, which may be introduced into cells, and which may be employed in methods of modifying a nucleic acid, methods of inhibiting the expression of a disease-associated gene which may be an oncogene (which may be BCR-ABL or Ras). The DNA or phage was immobilized on microtiter plates using affinity media as a method of detection.

Jamieson et al. did not teach the target DNA was GCAGAAGCC or GACGGCGCC, nor kits for the use of the invention supra, nor methods of treatment of cancer.

Rebar et al. (see the entire article) and Desjarlais et al. (see especially the abstract and introduction) taught a phage display system to select zinc finger proteins with altered DNA binding specificities by randomizing the amino acids at positions -1, +2, +3, and +6. Rebar et al. focused on the zinc finger 1 with 1 additional base from finger 2 in a 3 finger polypeptide.

Nardelli et al. taught (see the abstract and introduction) the randomization of fingers 1 and 2 of Krox-20, where finger 2 is chosen because it is essential for high affinity binding (see page 4139, top of column 2).

Jacobs taught (see especially figures 1 and 3, and tables I and III) that positions +4 and +7 were highly conserved for protein folding, suggesting the randomization of positions -1, +2, +3, and +6 as base contact positions or DNA recognition positions.

Thiesen et al. taught (see the introduction) the substitution of SP-1 into Kox-29 at finger 2 as means of substituting bases -1, +2, +3, +5 and +6.

Since zinc fingers bind in a general way, such that many different zinc fingers may bind a single target triplet DNA with varying degrees of affinity, the choice of a zinc finger which recognizes the target DNA GCAGAAGCC or GACGGCGCC merely recites a subclass of zinc fingers, and is not distinguished in any particular way in the claims nor in the specification so as to recite a species which can be distinguished from the zinc fingers of the preceding claimed invention. Kits for the use of the invention supra are obvious as is the claimed subject matter to which they refer, absent any evidence to the contrary.

It would have been obvious to one of ordinary skill in the art at the time applicant's invention was made to combine the teachings of Jamieson et al. Rebar et al., Thiesen et al., Jacobs, Nardelli et al. and Desjarlais et al. to produce the instant invention because they all were investigating the rules of selection of zinc fingers for DNA recognition and binding by studying the substitution of amino acids in the zinc fingers of well known polypeptides.

One of ordinary skill in the art would have been motivated to combine the teachings of Jamieson et al. Rebar et al., Thiesen et al., Jacobs, Nardelli et al. and Desjarlais et al. to produce the instant invention because the selection of zinc fingers to recognize and bind DNA molecules is known to depend on the sequence of amino acids that fit into the major groove of the DNA molecule, and each zinc finger recognizes and binds to a DNA triplet (usually). By altering the amino acid sequence, one can alter the DNA triplet which is bound. Understanding the rules

which govern that recognition and binding by altering the amino acid sequence or structure, or the corresponding DNA triplet which was bound, was the objective of Jamieson et al. Rebar et al., Thiesen et al., Jacobs, Nardelli et al. and Desjarlais et al.. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Jamieson et al. Rebar et al., Thiesen et al., Jacobs, Nardelli et al. and Desjarlais et al..

Conclusion

16. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1805 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
November 11, 1997

NANCY DEGEN
PRIMARY EXAMINER